RESULTS OF STUDY 154-120:

A total of 625 male and female patients were enrolled at 10 centers in the United States. Two additional patients were screened but never randomized. There were 311 patients (133 men, 178 women) randomized to trovafloxacin and 314 patients (137 men, 177 women) randomized to ofloxacin. Enrollment by center and the number of patients considered evaluable by the applicant is presented below:

		TROVAFLOXACIN		OFLOXACIN	
SITE	PRINCIPAL INVESTIGATOR	ENROLL	EVAL *	ENROLL	EVAL *
5003	James McCarty, M.D. Fresno, CA	3	3	3	3
5012	Z. A. Dalu, M.D. St Louis, MO	35	21 (60%)	35	26 (74%)
5068	Robert B. Jones, M.D. Indianapolis, IN	70	38 (54%)	72	46 (64%)
5069	David Martin, M.D. New Orleans, LA	27	18 (67%)	27	17 (63%)
5162	Myron Cohen, M.D. Chapel Hill & Raleigh, NC	29	21 (72%)	29	27 (93%)
5163	John Douglas, M.D. Denver, CO	20	13 (65%)	22	17 (77%)
5164	H. Hunter Handsfield, M.D. Seattle, WA	14	12 (86%)	14	11 (79%)
5165	Jane Schwebke, M.D. Birmingham, AL	50	35 (70%)	50	38 (76%)
5166	William McCormack, M.D. Brooklyn, NY	24	19 (79%)	23	17 (74%)
5167	Edwin Thorpe, Jr., M.D. Memphis, TN	39	24 (62%)	39	29 (74%)
	TOTAL**	311	204 (66%)	314	231 (74%)

*Number in parentheses represents the percent of patients evaluable by study center and then overall.

**Of the 311 trovafloxacin patients (133 men, 178 women), 204 were evaluable (105 men, 99 women) Of the 314 ofloxacin patients (137 men, 177 women), 231 were evaluable (111 men, 120 women).

COMMENT:
Clinical review of the patient line listings (CRTs) and spot checking of the CRFs showed that there were minimal differences in the sponsor's classification of outcome and the reviewer's classification. Specifically, there were approximately one or two

patients, both male and female, in both the trovafloxacin arm and the ofloxacin arm that could have been reclassified as evaluable, although technically their follow-up visit was at day 10 or 11. Spot checking did not disclose any serious differences, such as failures that were not recognized or reported. Within the limits of the CRT review and the random examination of the CRFs, no discrepancies were noted; thus, the applicant's data are accepted for review. The effect of accepting one or two additional patients as demonstrating eradication is to marginally raise the efficacy. Therefore, the reviewer accepts the applicant's analysis of the data.

REASONS FOR EXCLUSION OF PATIENTS FROM EVALUATION OF EFFICACY

KEY: M=male, F=female

	TROVAFLOXACIN			OFLOXACIN		
TOTAL ENROLLED	All	M	F	ALL	M	F
	311	133	178	314	137	177
Reason for Exclusion						
No pathogen	73	8	65 (37%)	54	10	44 (25%)
No follow-up visit	31	19	12	28	15	13
Concom antibiotic	2	1	1	1	1	0
Previously enrolled	1	0	1	0	0	0
EVALUABLE						
Bacteriological	204	105	99(56%)	231	111	120 (68%)

	TROVAFLOXACIN		OFLOXACIN	
	MALE	FEMALE	MALE	FEMALE
ENROLLED PATIENTS	133	178	137	177
BACTERIOLOGICALLY EVALUABLE PATIENTS	105 (79%)	99 (56%)	111 (81%)	120 (68%)

COMMENT:

As far as the issue of evaluable vs. nonevaluable patients, it is apparent that approximately 80% of all men (either treatment group) are evaluable. In contrast, there is a greater loss of women from the evaluable pool. The explanation for fewer evaluable women is that many more are screened because the disease can often be asymptomatic in women. The bigger question is that there is a difference between the proportion of trovafloxacin evaluable patients (56%) and the ofloxacin evaluable patients (68%) which should not have occurred by chance. Dr. Johnson at Pfizer commented that the study was conducted double-blind, and that all cultures were evaluated at a central laboratory. There is no obvious explanation for the greater percentage of negative cultures among the trovafloxacin female patients, but this has reduced the number of evaluable females on the test drug.

DEMOGRAPHIC CHARACTERISTICS for the enrolled population and the bacteriologically evaluable population are presented in the table below.

	TROVAFLOXACIN		OFLOXACIN	
	MALE	FEMALE	MALE	FEMALE
ENROLLED PATIENTS	133	178	137	177
Age (yr)				
Mean	26	25	27	24
Range				
Race				
Black	125 (94%)	159 (89%)	127 (93%)	159 (90%)
White	5	17	7	12
Other	3	2	3	6
Weight (kg)				
Mean	79	71	78	68
Range				

	TROVAFLOXACIN		OFLOXACIN	
	MALE	FEMALE	MALE	FEMALE
BACTERIOLOGICALLY EVALUABLE PATIENTS	105	99	111	120
Age (yr)				
Mean	27	24	27	24
Range				
Race				
Black	97 (92%)	89 (90%)	104 (94%)	107 (89%)
White	5	8	5	8
Other	3	2	2	5
Weight (kg)				
Mean	78	70	78	68
Range				

COMMENT:
At entry, the patient characteristics for all patients are balanced across the different treatment groups. The balance in demographic characteristics remains also among the bacteriologically-evaluable population as well.

CONCOMITANT MEDICATION:

Approximately 30 women in each arm were taking OCP, some treated for vaginitis. At the end of the follow-up visit about one-half of the patients received treatment for chlamydia.

BACTERIOLOGICAL OUTCOME IN BACTERIOLOGICALLY EVALUABLE PATIENTS

	TROVAFLOXACIN N = 204		OFLOXACIN N = 231	
EVALUABLE PATIENTS	MALE	FEMALE	MALE	FEMALE
	105	99	111	120
SITE OF INFECTION				
URETHRA	104	2	111	0
CERVIX	n/a	94	n/a	116
RECTUM	0	27	0	18
PHARYNX	5	9	4	8

COMMENT:
As would be expected, the major site of infection was urethra in men, cervix in women. Urethra was the site of infection in 104/105 evaluable trovafloxacin and 111/111 ofloxacin men, 1 trovafloxacin patient had gonorrhea involving only the pharynx (by culture). Cervix was the site of involvement in 94/99 evaluable trovafloxacin women; the other 5 had urethral (2), rectal (2) or pharyngeal (1) involvement. Among ofloxacin women, 116/120 had cervix as the primary site of involvement, while the remaining 4 had either rectal (2) or pharyngeal (2) involvement.

BACTERIOLOGICAL OUTCOME IN **MALES**:

ERADICATION RATES	TROVAFLOXACIN	OFLOXACIN
URETHRA	103/104 (99%)	111/111 (100%)
CERVIX	n/a	n/a
RECTUM	0/0	0/0
PHARYNX	5/5	4/4

BACTERIOLOGICAL OUTCOME IN **FEMALES**:

ERADICATION RATES	TROVAFLOXACIN	OFLOXACIN
URETHRA	2/2	0/0
CERVIX	93/94 (99%)	112/116 (97%)
RECTUM	27/27 (100%)	18/18 (100%)
PHARYNX	9/9	8/8

COMMENT:
The bacteriological results presented above indicate that trovafloxacin is 99% effective at eradicating gonorrhea from the urethra in men and cervix in women. The size of the study meets the recommended number for men but is slightly shy of the recommended number of 100 women. As noted earlier, another two could be considered

evaluble although their follow-up was marginally longer. This issue will be reconsidered after the results of Study 154-107 are reviewed.

In addition, the data are adequate to support approval of treatment of rectal gonorrhea in women. However, inadequate data have been submitted to support approval of the treatment of rectal gonorrhea in males or for the treatment of pharyngeal gonorrhea in either gender.

Penicillinase-Producing Isolates:

The applicant has requested that the labeling grant approval for both penicillinase-producing and non-producing isolates. Information on how many bacteriologically-evaluable patients had isolates that were penicillinase producing was not provided in the study report but was generated by the company as an additional analysis. The information was confirmed in Appendix 5 of the study report and is summarized below (numerator represents number of patients with penicillinase producing isolates; denominator represents number of bacteriologically-evaluable patients):

	Trovafloxacin	Ofloxacin
Males	15/105	14/111
Female	15/99	13/120

Among men, each of them had only one isolate (urethra). Among women, there were 7 trovafloxacin and 3 ofloxacin women who had two isolates each (cervix and rectum); thus there were 22 and 16 penicillinase-producing isolates from women, respectively. All of the penicillinase-producing isolates tested were susceptible to trovafloxacin. All of the penicillinase-producing isolates from bacteriologically-evaluable patients were eradicated.

Clinical outcome was reported by the applicant and is presented below:

CLINICAL OUTCOME IN **MALES:**

	TROVAFLOXACIN	OFLOXACIN
Cure	91/105 (87%)	102/111 (92%)
Improvement	12/105 (11%)	9/111 (8%)
Failure	2/105 (2%)	0/111
Asymptomatic	0	0

CLINICAL OUTCOME IN **FEMALES:**

	TROVAFLOXACIN	OFLOXACIN
Cure	65/99 (66%)	81/120 (68%)
Improvement	6/99 (6%)	16/120 (13%)
Failure	6/99 (6%)	4/120 (3%)
Asymptomatic	22 (22%)	19 (16%)

Intent-to-treat analyses of clinical outcome and bacteriological outcome were also performed by the sponsor, and patients who had missing values were counted as a persistence or eradication, respectively. Therefore, the ITT analyses showed consistently lower rates; however, they did not show a difference in outcome between the two arms which would have suggested that some bias or imbalance may exist.

USE OF CONCOMITANT ANTIBIOTICS
There appear to be only one or two patients per arm who used concomitant antibiotics during the study. One example is a patient who was prescribed SMX/TMP for sinusitis two days into the follow-up. Although trovafloxacin is being developed for the sinusitis indication also, the dosing regimen is more than the single dose given for GC. In addition, about one-half of the patients received treatment for Chlamydia after completion of the study.

STATISTICAL EVALUATION:
The applicant performed a 95% C.I. test for the study and the evaluable population actually fell within their planned + or - 10%. However, a 95% C.I. is irrelevant in this indication, where the lowest acceptable limit of the point estimate is 95%, and approximately 100 women and 100 men should be evaluated.

SAFETY RESULTS:
One female patient in the ofloxacin arm discontinued the study due to vomiting, it was not considered drug related.

There were 33 trovafloxacin patients and 27 ofloxacin patients who did not return for follow-up.

Adverse events were reported in 14% of the trovafloxacin patients and 15% of the ofloxacin patients, 8% in each arm were considered treatment-related. The table below summarizes the more common events. In addition, laboratory abnormalities were reported in approximately 15% of the patients.

	TROVAFLOXACIN	OFLOXACIN
ANY ADVERSE EVENT	44/311 (14%)	46/314 (15%)
Treatment Related Adverse Event	24/311 (8%)	24/314 (8%)
Discontinued due to Adverse Event	0	1/314

The following specific adverse events considered treatment related were reported.

	Trovafloxacin N = 311	Ofloxacin N = 314
Dry Mouth	1	0
Dizziness	5 (1.6%)	3 (1.0%)
Headache	1	2
Tongue paralysis	0	1
Insomnia	0	1
Somnolence	1	2
Altered bowel habit	0	1
Diarrhea	2	0
Dyspepsia	1	0
Nausea	0	3
Vomiting	1	1
Asthenia	1	1
Moniliasis	0	1
Vaginitis	5	9
Pruritus	4	2
Rash	3	1
Urticaria	1	0
Micturition frequency	1	0
total events	27	26

COMMENT:
The adverse event profile of the two regimens appears similar overall with perhaps the following suggested differences. Dizziness was noted in 5 Trovan and 3 ofloxacin patients, yet overall when headache, insomnia, somnolence etc are added there were 7 Trovan events vs. 9 ofloxacin events in the "neurologic"-type category. Vaginitis/moniliasis was reported by 5 Trovan patients vs. 10 ofloxacin patients (approximately 55% of the patients were females). Rash, pruritus or urticaria was noted in 8 Trovan patients vs. 3 ofloxacin patients. These observations need to be compared to the safety profile of Trovan overall in the review conducted by Dr. Coyne. Over 90% of the reported events were considered mild, no serious events were reported. However, for an overall conclusion regarding the safety profile of Trovan, including multiple dose use, the reader is referred to the comprehensive safety review by Dr. Coyne.

Laboratory changes, defined as clinically significant, were reported to be identified in 15% of Trovan patients and 17% of ofloxacin patients. It should be noted that approximately 80% of the enrolled patients had laboratory testing performed before and after treatment to assess for changes in laboratory values following a single dose of trovafloxacin or ofloxacin.

	Trovafloxacin	Ofloxacin	Definition of Clin. Significant. (relative to normal)
Any abnormality	35/236 (15%)	42/242 (17%)	
Hemoglobin	0	0	(< 80% LLN)
Hematocrit	0	0	(< 80% LLN)
RBC	0	0	(< 75% LLN)
Platelets	0	0	(<75% to >125%)
WBCs	2	3	(<75% to >125%)
Bilirubin	1	0	(> 1.5 x ULN)
ALT	0	0	(> 2 x ULN)
AST	0	0	(> 2 x ULN)
Protein	0	0	(<0.9 or >1.1)
Albumin	0	0	(<0.8 to >1.2)
BUN	0	0	(> 1.3 x ULN)
Creatinine	0	0	(> 1.3 x ULN)
Sodium	0	0	(< 95 or >1.05)
Potassium	0	1	(<0.9 or >1.1)
Chloride	0	0	(<0.9 or >1.1)
Bicarbonate	0	0	(<0.9 or >1.1)
Urine RBC	14	16	(> 6/HPF)
Urine WBC	12	19	(> 6/HPF)
Urine SG	2	6	(<1 or > 1.035)
Urine pH	0	0	(<0.9 or >1.1)
Urine Protein	3	2	(> 2+)
Urine Glucose	0	0	(> 2+)
Urine Ketones	1	2	(> 1+)

COMMENT:
There were relatively few laboratory abnormalities noted; the majority related to Urine WBC and RBC in both groups.

STUDY 154-107:

TITLE:
An open, randomized, non-comparative, single center dose-ranging study of trovafloxacin (CP-99,219) in the treatment of uncomplicated gonorrhea.

PURPOSE:
To assess the safety and effectiveness of three different doses of trovafloxacin in the treatment of uncomplicated gonorrhea in male and female patients.

STUDY DESIGN:
The study was a dose-ranging, randomized, single-center trial conducted in the USA, comparing a single dose of trovafloxacin 50 mg, 100 mg or 200 mg. The plan was to enroll approximately 30 male and female patients.

STUDY CONDUCT: March 31, 1994 to July 11, 1994

INCLUSION AND EXCLUSION CRITERIA:
analogous to study 154-120

DRUGS AND DOSAGE REGIMEN:

Trovafloxacin 50 mg, 100 mg or 200 mg orally, single-dose administered as a powder to be reconstituted to suspension or as a tablet

All drug was administered under direct observation. Dosing was to be done two hours before or two hours after a meal or use of antacid.

A randomization schedule was provided, with different blocks of numbers for male patients and female patients (presumably to ensure adequate enrollment of each gender).

CONCOMITANT MEDICATIONS:
analogous to study 154-120

EVALUATION OF EFFICACY:
analogous to study 154-120

SAFETY ASSESSMENT:
analogous to study 154-120

STUDY RESULTS:

A total of 39 men and women were enrolled by Dr. Edward Hook at Birmingham, Alabama. The number of patients randomized to each group, excluded from evaluation and evaluable for assessment of efficacy is summarized in the table below:

	Trovafloxacin Doses					
	50 mg		100 mg		200 mg	
	male	female	male	female	male	female
Randomized	4	7	6	8	6	8
No pathogen	0	2	0	3	1	2
No follow-up	0	1	0	0	1	0
Bacteriologically Evaluable	4	4	6	5	4	6

DEMOGRAPHIC DATA for all enrolled subjects:

	Trovafloxacin Doses					
	50 mg		100 mg		200 mg	
	male	female	male	female	male	female
Age: mean	23	24	25	23	24	28
range						
Race: black	4	6	5	8	6	8
other	0	1	1	0	0	0
Weight: (kg)						
mean	72	64	77	79	77	69
range						

The demographic data on the bacteriologically-evaluable subjects were comparable.

BACTERIOLOGICAL OUTCOME

	Trovafloxacin Doses					
	50 mg		100 mg		200 mg	
	male	female	male	female	male	female
Bacteriologically Evaluable	4	4	6	5	4	6
Site of infection						
Urethra	4	0	6	0	4	0
Cervix	0	4	0	5	0	5
Pharynx	0	1	3	1	1	1
Rectum	0	1	0	1	0	3

Note that all patients had eradication of *Neisseria* isolates from all sites, thus the total eradication rates supporting the efficacy of 100 mg of trovafloxacin are presented below, based on combining the results from the 50 mg and 100 mg groups. It is recognized that the study formulations included powder and tablet.

	MALES	FEMALES
URETHRA	10/10	0
CERVIX	0	9/9
PHARYNX	3/3	2/2
RECTUM	0	2/2

SAFETY EVALUATION:
Two patients in the 200 mg group reported somnolence(1) and asthenia (1). No other treatment related events were noted.

	Trovafloxacin N = 37	Definition of Clinically Dsginifant (relative to normal)
Any abnormality		
Hemoglobin	0	(< 80% LLN)
Hematocrit	0	(< 80% LLN)
RBC	0	(< 75% LLN)
Platelets	0	(<75% to >125%)
Neutrophil	2	(<75% to >125%)
Eosinophil	1	(> 10%)
Bilirubin	0	(> 1.5 x ULN)
ALT	1	(> 2 x ULN)
AST	1	(> 2 x ULN)
Protein	1	(<0.9 or >1.1)
Albumin	0	(<0.8 to >1.2)
BUN	0	(> 1.3 x ULN)
Creatinine	0	(> 1.3 x ULN)
Sodium	0	(< 95 or >1.05)
Potassium	6	(<0.9 or >1.1)
Chloride	0	(<0.9 or >1.1)
Bicarbonate	0	(<0.9 or >1.1)
Urine RBC	5	(> 6/HPF)
Urine WBC	5	(> 6/HPF)
Urine SG	0	(<1 or > 1.035)
Urine pH	0	(<0.9 or >1.1)
Urine Protein	0	(> 2+)
Urine Glucose	0	(> 2+)
Urine Ketones	0	(> 1+)
Urine Casts	0	(> 1)

COMMENT:
Several patients had elevations in potassium, presence of urinary RBC and WBC. Two patients had neutrophils less than 1000/mm3. These findings need to be taken in context of the overall safety profile of this agent from other studies.

SUMMARY AND RECOMMENDATIONS:

Two clinical studies were conducted, a dose ranging study 154-107 testing 50 mg, 100 mg or 200 mg or trovafloxacin in a total of 39 male and female patients and study 154-120 comparing 100 mg of trovafloxacin to 400 mg of ofloxacin in 625 male and female patients.

The eradication rates for *Neisseria gonorrhoeae* in bacteriologically evaluable patients from each of the studies is summarized in the table below.

BACTERIOLOGICAL OUTCOME IN MALES treated with trovafloxacin:

	154-107	154-120	TOTAL
URETHRA	10/10	103/104	113/114 (99%)
PHARYNX	3/3	5/5	8/8
RECTUM	0	0	0

BACTERIOLOGICAL OUTCOME IN FEMALES treated with trovafloxacin:

	154-107	154-120	TOTAL
CERVIX	9/9	93/94	102/103 (99%)
RECTUM	2/2	27/27	29/29
PHARYNX	2/2	9/9	11/11
URETHRA	0	2/2	2/2

Thus, based on these results, it is recommended that trovafloxacin be approved for the treatment of uncomplicated gonorrhea (cervical and urethral) at a dose of 100 mg orally. In addition, the treatment of rectal gonorrhea in women may be approved. The data submitted are inadequate to approve treatment of rectal gonorrhea in males and the treatment of pharyngeal gonorrhea in any gender.

The applicant has provided data on at least 10 penicillinase-producing isolates of *N. gonorrhoeae* that were treated and eradicated, per gender. These isolates were susceptible to trovafloxacin. To date, the Division has not placed information on the penicillinase status of *Neisseria gonorrhoeae* in the approved labeling of any quinolone antimicrobial, because this mechanism of resistance is not linked to resistance to quinolones. Thus, the approved labeling for trovafloxacin should not mention the penicillinase status of the isolates at this time.

PROPOSED LABELING REVISION:

/S/

Carmen DeBellas, R.Ph.

/S/

Renata Albrecht, M.D.

cc: NDA 20-759
HFD-590
HFD-590/DepDir/Albrecht
HFD-520/Pharm/Ellis
HFD-520/Micro/Altaie
HFD-590/Chem/
HFD-590/CSO/Fogarty
Clinical Review GC
HFD-590/ LEISSA

Concurrence:
HFD-590/DD/Goldberger /S/ 7/13/98
HFD-590/TL/Leissa /S/ 7/13/98

MEDICAL REVIEW OF NDA 20-759, 20-760

Applicant:
Pfizer Inc.
Central Research Division
Eastern Point Road
Groton, CT 06340
Contact person: Ronald Trust, Ph.D., M.B.A.

NOV 19 1998

Date of submission:	December 27, 1996
Date received by reviewer:	January 14, 1997
Date review begun:	September 15, 1997
Date draft of review completed:	December 2, 1997
Date review received from secondary reviewer:	October 21, 1998
Date review completed:	November 17, 1998

Currently approved indications: none

Material reviewed: Electronic submission

REGULATORY BACKGROUND

(b)(4)

[redacted]

PROPOSED LABELLING

DRAFT LABELING

[redacted]

REGULATORY GUIDANCE

A. 1992 DAIDP Points to Consider

1. Establish equivalence or superiority to an approved product in one statistically adequate and well-controlled, multicenter trial
2. At least 50% of the clinically evaluable patients must be bacteriologically evaluable

B. IDSA/FDA guidelines [Clin Infectious Dis 1992; 15(S1): 53-61]

1. Subjects (b)(4) are considered adults except when age-specific safety issues need to be considered.

2. Patients should be stratified at enrollment according to the type of pelvic inflammatory disease (PID)--uncomplicated or complicated

3. A diagnosis of PID must be confirmed by meeting clinical and microbiologic criteria and/or by laparoscopy and/or endometrial biopsy.

4. Patients who are seropositive for syphilis should be excluded from the study and considered to have an indeterminate outcome.

5. It is expected that the clinical cure rates for acute PID and tubo-ovarian abscess (TOA) will be (b)(4) respectively.

6. Treatment for acute PID due to *N. gonorrheae* and mixed anaerobes must be given parenterally for at least 4 days, and then for at least 48 hours after a favourable clinical response. Antichlamydial therapy should be given for a total of 14 days. The minimum duration of parenteral therapy for TOA should be 7 days.

7. Patients must be followed for 2-4 weeks after therapy to be eligible for evaluation of efficacy. The presence of *C. trachomatis* or *N. gonorrhoeae*, even in the absence of symptoms, is indicative of the failure of treatment.

NON-CLINICAL STUDIES

(b)(4)

Animal Pharmacology/Toxicology
See Toxicology review by A. Ellis, Ph.D.

Microbiology
See Microbiology review by S. Altaie, Ph.D.

CLINICAL STUDIES

Human Pharmacokinetics/Pharmacodynamics
See full review by P. Colangelo, Ph.D.
Trovafloxacin's biologic half-life is approximately 9 to 11 hours. The mean bound fraction in plasma samples is approximately (b)(4) Steady state concentrations are achieved by the third daily dose. In adult subjects, the pharmacokinetics of trovafloxacin are not affected by age or gender. Peak blood level (Cmax) of trovafloxacin at a 200 mg oral dose is 2.5 ug/mL and tissue/ serum concentration ratios in the cervix after single and multiple doses of trovafloxacin 200 mg were 0.5 ug/mL (3-29 hr postdose) and 0.6 ug/mL (3-16 hr postdose), respectively.

Human Clinical Experience
The efficacy and safety of trovafloxacin for several indications was evaluated in 45 phase I studies and 31 phase II/III studies.

INTRODUCTION TO CLINICAL TRIALS

The applicant submitted 2 pivotal clinical trials in support of this indication- a randomized, comparative trial to assess the efficacy of trovafloxacin in ambulatory patients with PID, and the second, a randomized, double-blind, comparative trial to evaluate trovafloxacin for the treatment of hospitalized patients with complicated PID.

Study 154-122

Title: "A randomized, multi-center, investigator-blind, comparative trial of CP-116,517/CP-99,219 and cefoxitin/doxycycline for the treatment acute pelvic inflammatory disease in hospitalized subjects"

Primary objective

To compare the efficacy and safety of alatrofloxacin/trovafloxacin and cefoxitin/doxycycline in the treatment of hospitalized subjects with acute pelvic inflammatory disease.

Study Design Summary	
Location	USA (36 sites), Republic of South Africa (5 sites)
Patients	16 years and older
Study dates	5 June 1995 - 9 May 1996
Amendment dates	March 21, 1995; August 18, 1995
Study dose and duration	Alatrofloxacin IV and Trovafloxacin orally 200 mg qd for 14 days
Comparator	Cefoxitin 2gm IV q 6h PLUS Doxycycline 100mg IV q 12h then doxycycline 100mg for total 14 days
Blinding	investigator-blind
Method of assignment	1:1 random assignment at each center
Primary efficacy variable	clinical outcome at visit 4
Safety variables	clinical signs and symptoms, laboratory results
Therapy evaluation, days (window)	
Baseline	1 (within 48 hours)
Visit 2	72 hours after initiation of treatment
End of treatment-EOT	14 (14-20)
End of study-EOS	week 4-6 after initiation of therapy
Number of subjects randomized	79 (alatrofloxacin/trova)/ 79 (cefoxitin/doxycycline)

STUDY POPULATION

Inclusion criteria

1. Hospitalized women. Women of childbearing potential (i.e., not surgically sterile ≤one year post menopausal) with a negative urine or serum gonadotropin pregnancy test immediately prior to entry in the study and using adequate contraception both during and for one month after the end of treatment.
2. At least 16 years of age.
3. Presumptive diagnosis of acute PID. While subject enrollment may have been based on a diagnosis established solely on clinical grounds, the diagnosis may, at the investigator's discretion, have been confirmed by laparoscopy or by endometrial biopsy (with the histological finding of polymorphonuclear leukocytes and/or plasma cells). Clinical and/or laparoscopic staging followed Hager's criteria (see below). Clinical diagnosis must have been substantiated by all of the following (a through c):

a. Lower abdominal tenderness, with or without rebound (unilateral or bilateral)
b. Tenderness upon motion of the cervix and uterus
c. Adnexal tenderness (unilateral or bilateral)
d. In addition, at least one of the following must have been present:
   (1) Evidence suggesting cervical infection with *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*:
      (a) Mucopurulent endocervicitis
      (b) Positive Gram stain for Gram-negative intracellular diplococci
      (c) Endocervical Gram stain demonstrating ≥ 10 WBC/oil immersion field (x 1,000)
      (d) Positive result in a rapid diagnostic screening test for *C. trachomatis*
   (2) Purulent material obtained by culdocentesis or laparoscopy (if performed)
   (3) Inflammatory mass suspected on bimanual examination and confirmed by ultrasound
   (4) Fever (admission temperature ≥ $38^{O}C$ [$100.4^{O}F$])
   (5) Leukocytosis (WBC ≥ 10,500/mm^3)
   (6) Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
   (7) Plasma cell endometritis (> 1 plasma cell/HPF on endometrial biopsy [if performed])

Medical officer's comments:
The medical reviewer agrees with the criteria as outlined, which are standard diagnostic criteria for PID.

GRADING OF PID BY CLINICAL EXAMINATION

I. Uncomplicated: Limited to tube(s) and/or ovary(ies)
   A. Without pelvic peritonitis
   B. With pelvic peritonitis
II. Complicated: Inflammatory mass or abscess involving tube(s) and/or ovary(ies)
   A. Without pelvic peritonitis
   B. With pelvic peritonitis
III. Spread to structures beyond pelvis, i.e., ruptured tubo-ovarian abscess

NOTE: Subjects with Grade III PID were excluded from the study.

SEVERITY OF DISEASE BY LAPAROSCOPIC EXAMINATION

Mild:	Erythema, edema, no spontaneous purulent exudate;* tubes freely moveable
Moderate:	Grossly purulent material evident; erythema and edema more marked. Tubes may not be freely moveable, and fimbria stoma may not be patent.
Severe:	1. Pyosalpinx or inflammatory complex 2. Abscess+

* The tubes may have required manipulation to produce purulent exudate.
+ The size of any pelvic abscess should be measured.

Exclusion criteria

1. Pregnant women, nursing mothers, or women of childbearing potential not practicing adequate means of contraception
2. Known or suspected hypersensitivity or intolerance to any quinolone antibiotic, clindamycin, or lincomycin.
3. Outpatients.
4. Suspected ruptured tubo-ovarian abscess (TOA) on admission.
5. Intrauterine device in place which the subject refuses to have removed within 24 hours of entry into the study.
6. History of pelvic or abdominal surgery within the 30 days prior to admission.
7. Presence of any other infection at enrollment that may have required treatment with an antibiotic other than the study drugs. A single dose regimen for treatment of trichomoniasis after clinical response had been demonstrated was acceptable.
8. Treatment with any systemic antibiotic for 24 hours or longer within two weeks prior to entry into the study, unless there was documented evidence of clinical failure.
9. Treatment with another investigational drug within 30 days prior to entry into the study.
10. Evidence of significant gastrointestinal or other conditions which may have affected drug absorption.
11. Evidence or history of clinically significant hematologic, renal (i.e., serum creatinine greater than 2.0 mg/dL or creatinine clearance or immunologic compromise (i.e., neutropenia [total white blood cell count 1000/mm^3] or known AIDS).
12. History of epilepsy or seizures.

Medical officer's comments:
The reviewer agrees with criteria as outlined. Patients with trichomoniasis during the study could receive a single dose of therapy with an appropriate agent after the assessment of clinical and microbiologic outcome; these patients were not excluded and were eligible for evaluability.

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SUBJECT EVALUATION VISITS

Visit 1 at day 1 (Baseline)
Within 24 hours prior to the start of therapy, baseline visit assessments included a history and a targeted physical examination, a serum or urine gonadotropin pregnancy test for women of childbearing potential, a standard panel of blood and urine safety tests, and a serologic test for syphilis (FTA or RPR).

In an attempt to standardize and semiquantitate clinical severity of PID and to assess the clinical response to therapy, a Clinical Tenderness Score (CTS) was used (see below). Upon entry into the study, the CTS (maximum CTS = 42), extent of fever, and white blood cell count were determined for each subject. The subject's body temperature and CTS were also assessed at the follow-up visits, two and four to six weeks following initiation of therapy.

CLINICAL TENDERNESS SCORE FOR PID (MAXIMUM = 42)

A. The following areas were assessed:
   1. Abdominal tenderness (direct); score each quadrant
   2. Abdominal tenderness (rebound); score each quadrant
   3. Cervical motion tenderness
   4. Uterine tenderness
   5. Adnexal tenderness, left

6. Adnexal tenderness, right
7. Adnexal mass, left
8. Adnexal mass, right

B. Scoring

1. Tenderness
   - 0 = tenderness absent
   - 1 = tenderness described by subject but not manifested by changes in facial expression or abdominal muscle tone
   - 2 = tenderness resulting in altered facial expression or abdominal muscle tone
   - 3 = tenderness causing observable marked distress

2. Adnexal masses, scored by size
   - 0 = no mass
   - 1 = mass < 2 cm
   - 2 = mass 2-5 cm
   - 3 = mass >5 cm

While they may have been obtained by use of culdocentesis, the following specimens were required from each subject (a and b):

a. Culture by swab of the endocervix and rectum for *N. gonorrhoeae, and C. trachomatis* from the endocervix by culture (strongly recommended), antigen detection, or other acceptable rapid nonculture test.

b. endometrial material for anaerobic and facultative culture and for isolation of *N. gonorrhoeae, and C. trachomatis* by culture (strongly recommended), antigen detection, or other acceptable rapid nonculture test. All isolates of C. trachomatis were to be frozen at -70°C for possible susceptibility testing later.

c. For those subjects undergoing laparoscopy (at the investigator's discretion), a directed culture from the fallopian tube was to be obtained for aerobic and anaerobic cultures and for isolation of N. *gonorrhoeae. C. trachomatis* was to be sought by culture, antigen detection, or other acceptable rapid nonculture test. Peritoneal fluid was to be cultured for the same microorganisms.

Visit 2 at 72 hours

Failure to demonstrate response at 72 hours after initiation of therapy (i.e., reduction in the CTS, and/or reduction in fever, and/or reduction in white blood cell count) constituted clinical failure, and the investigator was to remove the subject from study treatment and institute alternative treatment. The battery of blood and urine tests performed at baseline was repeated.

Switching from intravenous to oral therapy

The subject's need for continued intravenous therapy was checked daily between days 3 and 7 of therapy. It was appropriate to switch to oral therapy if:

a. Resolution of fever (based on daily maximum temperature) and reduction in white blood cell count, ESR, and CRP were documented

b. Improving CTS noted

Visit 3 at 2-4 days following completion of therapy

Endocervical and rectal specimen cultures for *N. gonorrhoeae*, and endocervix culture (strongly recommended), antigen detection, or other acceptable rapid non-culture test *for C. trachomatis* were repeated. At the investigator's discretion, endometrial biopsy could be repeated for

anaerobic and facultative culture and for isolation *of N. gonorrhoeae*. Bacteriological response of *N. gonorrhoeae* and *C. trachomatis* was based on the assessments at visits 3 and 4.

The battery of blood and urine tests performed at baseline was repeated and an interval sexual history was obtained.

On the assumption that some investigators would perform a repeat endometrial biopsy at this visit, the primary assessment of bacteriological response of anaerobic and aerobic bacteria was made at this visit.

Visit 4 at 2-4 weeks following completion of therapy
Visit 4 was the primary efficacy endpoint for clinical response and final bacteriological response of N. *gonorrhoeae* and C. *trachomatis.*

Endocervical and rectal specimens were assessed for N. *gonorrhoeae and C. trachomatis* (endocervix only). Endometrial biopsy *was* not required at this visit. Other procedures performed at visit 4 included recording of interval sexual history, vital signs, adverse events and repeat of the battery of blood and urine tests performed at baseline and at visits 2 and 3.

Medical officer's comments:
The reviewer agrees with the overall design and notes that the timing of visits, including the TOC visit, was consistent with the IDSA/FDA guidelines. The guidelines note that interim analyses could be performed to assess clinical response 72 hours after the start of therapy and 2-4 days after the completion of therapy. Patients with *N. gonorrhoeae* or C. *trachomatis* isolated at the final evaluation, even in the absence of symptoms, were considered treatment failures.

Susceptibility testing
Susceptibility to CP-99,219, ofloxacin, and clindamycin was determined by disk diffusion and minimum inhibitory concentrations (MICs) for all pathogenic isolates (except *C. trachomatis*), whether at baseline or at follow-up.
Criteria for determining susceptibility to the study drugs ("susceptibility breakpoints") are summarized below.

	Trovafloxacin		Ofloxacin		Clindamycin	
Criteria	MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)	MIC (µg/mL)	Zone Diameter (mm) (5 µg Disk)	MIC (µg/mL)	Zone Diameter (mm) (2 µg Disk)
Susceptible (For *N. gonorrhoeae*)	≤ 2	≥15	≤ 2 (≤ 0.25)	≥ 16 (≥ 31)	≤ 0.5	≥ 21
Intermediate (For *N. gonorrhoeae*)	4	11-14	4 (-)	13-15 (-)	1-2	15-20
Resistant (For *N. gonorrhoeae*)	≥8 (-)	≤ 10 (-)	≥ 8	≤ 12	≥4	≤ 14

Note: Results using the 10 µg disks were not available during the study report period.
(-) No intermediate or resistant strains of *N. gonorrhoeae* currently identified.

Clinical Evaluations

On the basis of the investigator's assessments of the CTS, extent of fever, and white blood cell count, clinical efficacy was classified by the sponsor at two interim timepoints (72 hours after the initiation of therapy and 2-4 days following completion of therapy), with a final classification at 2- 4 weeks following completion of therapy. The following guidelines were used:

Interim assessments

a. *Presumptive clinical cure*
   1) Reduction of the CTS by ≥ 70% AND
   2) Resolution of fever and leukocytosis

b. *Presumptive clinical improvement*
   1) Reduction of the CTS by 30-70% AND
   2) Resolution of fever and leukocytosis

c. *Unsatisfactory response*
   1) Reduction of the CTS by < 30% within 2-4 days following completion of therapy AND
   2) Persistence of fever and/or leukocytosis

d. *Unevaluable response*
   1) Subject's withdrawal from the study for other than clinical failure
   2) Institution of an additional antibiotic for the treatment of an infection unrelated to PID
   3) Erroneous diagnosis
   4) Surgical intervention during the first 48-72 hours of therapy (**NOTE:** Subjects requiring such surgery after 72 hours were considered clinical failures).

In addition, failure to demonstrate response at 72 hours after initiation of therapy constituted clinical failure.

Final assessment

The overall clinical response was based on the global assessment of the subject by the investigator at visit 4 (2-4 weeks following completion of therapy). The potential outcomes were:

a. *Clinical cure*
   1) Reduction of the CTS and mass score by ≥70% AND
   2) Resolution of fever and leukocytosis AND
   3) No known clinical recurrence within 2-4 weeks following completion of therapy

b. *Clinical failure*
   1) Reduction of the CTS and mass score of < 70% OR
   2) Persistence of fever and/or leukocytosis OR
   3) Recurrence of signs and symptoms of PID within 2-4 weeks following completion of therapy OR
   4) Therapy required for longer than 14 days

Bacteriological Evaluations
The bacteriological response was determined 2-4 days following completion of therapy and 2-4 weeks following completion of therapy. Definitions of bacteriological response were as follows:

a. *Satisfactory response*
1) Eradication of *N. gonorrhoeae* and *C. trachomatis*, and actual or presumptive eradication of anaerobic and aerobic bacteria from the endometrium at the 2-4 day post-therapy assessment (determined by performance of repeat endometrial biopsy). If cultures were obtained at repeat endometrial biopsy, bacterial eradication could be determined. Without repeat endometrial biopsy, presumptive bacteriological eradication was based on the assessment of the subject's clinical response, AND

2) Eradication of *N. gonorrhoeae* and/or *C. trachomatis* from the endocervix (and rectum, if applicable, for *N. gonorrhoeae*) at the 2-4 week post-therapy assessment

b. *Unsatisfactory response*-Persistence of *N. gonorrhoeae* or *C. trachomatis* at either of the above assessments or actual or presumptive persistence of anaerobic or aerobic bacteria at the 2-4 day post-therapy assessment (determined by performance of repeat endometrial biopsy). If cultures were obtained at repeat endometrial biopsy, bacterial eradication could be determined. Without repeat endometrial biopsy, presumptive bacteriological eradication was based on the assessment of the subject's clinical response.

Indeterminate (for evaluable subgroup):
a. no baseline causative pathogen isolated
b. relevant post-baseline cultures not obtained, unless the lack of such cultures results from concomitant antibiotic use due to bacteriological persistence
c. concomitant antibiotic use for treatment of an intercurrent illness

Medical officer's comments:
The reviewer agrees with the definitions as outlined by the applicant.

Applicant's Criteria for Clinical evaluability (from study report)
Subject evaluability was based on data collected at Visit 4. If any of the following was present, the subject was considered <u>non-evaluable</u> for clinical efficacy:

1. Study medication discontinued, for any reason other than insufficient therapeutic effect, before the protocol specific minimum requirement (7 days)

2. Treatment with any systemic antibiotic for 24 hours or longer within 2 weeks prior to enrollment unless clinical failure.

3. Concomitant antibiotic prescribed at any time before the Visit 4 assessment that was potentially effective against the condition under study. The use of concomitant antibiotic therapy due to insufficient therapeutic effect of the study medication was not a reason for exclusion from the clinically evaluable subjects subset.

4. Intercurrent Illness whose clinical course confounded the clinical evaluation of the disease or condition under investigation. In order to be evaluable, a subject must have had an assessment in the Visit 4 analysis window, unless:

    - the subject was given an antibiotic for insufficient response at any time during study, up to and including the last day of the Visit 4 analysis window, or
    - the subject was discontinued due to lack of efficacy,

SCHEDULE OF STUDY VISITS AND PROCEDURES

STUDY DAYS

			Posttherapy	
	Baseline Day 1	Visit 2 72 h	Day 14	Visit 3 Days 16-18	Visit 4 Days 28-42
Treatment	X	———	X		
Compliance Checks		X		X	X
Informed Consent	X				
Demographic Information	X				
Targeted Physical Examination	X				
Concomitant Medication	X	X		X	X
Vital Signs	X	X		X	X
Assessments					
Clinical[a]	X	X		X	X
Culdocentesis, Endometrial Biopsy, and/or Laparoscopy[b]	X			(X)[c]	
Laboratory					
1. Hematology	X	X		X	X
2. Serum Chemistry	X	X		X	X
3. Urinalysis	X	X		X	X
4. Microbiology					
a. *N. gonorrhoeae* cultures	X			X	X
b. *C. trachomatis* cultures or assays	X			X	X
c. Anaerobic/aerobic cultures	X			(X)[c]	
5. FTA or RPR	X				
6. Pregnancy Test	X				
Adverse Events	X	X		X	X

[a] Assessments to be done daily during hospitalization
[b] Dependent upon which procedure(s) is(are) performed; endometrial biopsy required at baseline for microbiology (with histology optional)
[c] *At investigator's discretion*

- the subject had surgical intervention on Day 4 or later, or the investigator's clinical assessment was failure before Visit 4.

Applicant's Criteria for Bacteriological Evaluability (from study report)

If any of the following was present, the subject was considered non-evaluable for bacteriological efficacy.

1. No baseline causative *pathogen (N. gonorrhoeae, C. trachomatis* and/or pathogenic anaerobic or aerobic bacteria) was isolated and the subject did not have a positive non-culture chlamydial test at baseline.

2. The baseline culture (and non-culture chlamydial test) was done more than 2 calendar days before the first dose of study medication.

3. No culture (or non-culture chlamydial test) obtained at Visit 4 unless:

   - The subject was given an antibiotic for insufficient response, at any time up to and including the last day of the evaluable End of Study analysis window, or
   - The subject had a baseline pathogenic anaerobic or aerobic bacteria and the investigator's clinical response was recorded in the appropriate window.
   - The subject had a baseline pathogenic anaerobic or aerobic bacteria and the investigator's clinical response was failure prior to the End of Study window.

Medical officer's (MO) evaluability criteria

A. The primary efficacy variable is clinical response at the 4-6 week visit.

Patients were clinically non-evaluable if:

- insufficient therapy ---MO accepted patients who received at least 10 days of the study drug unless they were clinical failures early in the course of treatment
- unprotected sexual contact during study
- no clinical assessment 2-4 weeks after completion of study therapy
- positive serologic test for syphilis (indeterminate status)
- patients who received antibiotics within 2 weeks prior to study initiation
- IUD in place >24 hours after initiation of study therapy
- missing data and data outside study windows
- no baseline clinical assessment
- incorrect baseline diagnosis
- concomitant antimicrobial therapy during study unrelated to PID

B. Clinical failures will be those patients who:

- require surgery after 72 hours of study therapy
- clinically cured but bacteriologic failure
- insufficient therapy with study drug due to poor clinical response
- required concomitant systemic antimicrobial therapy due to poor clinical response or persistent pathogen
- subjects who were given alternate treatment due to poor response to the study drug or persistent pathogen were considered evaluable

C. Bacteriologically non evaluable:

The reviewer agrees with the applicant's criteria.

Statistical considerations
Assuming the clinical cure rate for the reference drug was 90%, the number of subjects required for each treatment group to ensure with 80% probability that the 95% confidence limits for the true difference in efficacy does not exceed 10% was 142 subjects per treatment group. The planned enrollment of 300 subjects was statistically adequate (under the assumption of a 90% cure rate for the comparative group). All statistical tests of significance were performed as two-sided tests (unless otherwise specified). No adjustments were made to significant levels for multiple endpoints on the same data. Baseline comparability of the treatment groups was assessed for age, race, and weight.

The primary efficacy endpoints were clinical and bacteriological responses at visit 4, four to six weeks following initiation of therapy. Modified "intent to treat" and "evaluable" clinical analyses were performed, comparing clinical and bacteriologic outcomes four to six weeks following initiation of therapy. The Cochran-Mantel-Haenzel test controlling for center were used to compare the treatments for clinical and bacteriological response. Also, 95% confidence intervals were produced for the difference between treatment effects for cure and eradication rates.

Criteria for Safety evaluation
Adverse events including serious adverse events were monitored up to visit 4, four to six weeks following initiation of therapy. Serious adverse events were monitored throughout the study and for 30 days after the last dose of study drug.

The clinical laboratory tests outlined below were performed at baseline and on visits 2 and 3.

- Hemoglobin, hematocrit, red blood cells, white blood cells, differential count, platelets, and ESR.
- AST, ALT, total bilirubin, LDH, alkaline phosphatase, urea, creatinine, total protein, albumin, sodium, potassium, bicarbonate, chloride, and random blood glucose, and C- reactive protein.
- Microscopy and urine chemistry (protein, glucose, ketones, bilirubin, pH, urobilinogen, blood and nitrate).

INVESTIGATORS AND STUDY SITES

COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
United States	5248	Carol Terregino, MD
	5601	James McGregor, MD
	5602	Stanley Gall, MD
	5604	James West, MD
	5609	Harvey Friedenson, MD
	5748	David Baker, MD
	5749	Gregory Fossum, MD
	5750	David Hemsell, MD
	5751	Abner Korn, MD
	5752	Maurizio Maccato, MD
	5756	Kevin Huddleston, MD
	5757	James Van Hook, MD
	5758	Bernard Gonik, MD
	5759	Richard Sweet, MD
	5763	Rebecca Ryder, MD
	5764	Chong Chang, MD
	5765	Blane Crandall, MD
	5766	Sebastian Faro, MD
	5767	Javier Gutierrez, MD
	5768	Peter Marsh, MD
	5805	Robert Holley, MD
	5866	William Koltun, MD
	5904	Richard Derman, MD

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COUNTRY	CENTER	PRINCIPAL INVESTIGATOR
	5905	Harold Wittcoff, MD
	5906	Dean Coonrod, MD
	5907	Joseph Mortola, MD
	5909	Elizabeth Trupin Campbell, MD
	5919	Mickey Karram, MD
	5920	Harrihar Pershadsingh, MD
	6003	John Larsen, MD
	6109	Mark Martens, MD
	6327	Janice Bacon, MD
	6377	Cheryl Walker, MD
	6378	Edward Zelnick, MD
	6390	Michael Margolis, MD
	6391	Howard Offenberg, MD
South Africa	6506	Peter De Jong, MD
	6507	Hendrik Cronje, MD
	6508	Cornelius Prins, MD
	6509	Barend Lindeque, MD
	6510	Johan DeSouza, MD

RESULTS

PATIENT ENROLLMENT AND DISPOSITION

Table122.1 Patients evaluable (per applicant) by center

		Trovafloxacin			Cefoxitin/doxycycline		
center ID	total randomized	enrolled	evaluable	% evaluable	enrolled	evaluable	% evaluable
5248	2	1	0	0	1	0	0
5601	2	2	1	50	0	0	0
5602	2	1	1	100	1	1	100
5749	1	0	0	0	1	0	0
5750	5	3	1	33	2	2	100
5751	3	1	0	0	2	1	50
5752	6	2	1	50	4	1	25
5754	6	3	1	33	3	1	33
5756	3	1	0	0	2	2	100
5758	4	2	1	50	2	2	100
5763	4	2	1	50	2	0	0
5765	1	1	0	0	0	0	0
5768	1	1	1	100	0	0	0
5805	1	1	0	0	0	0	0
5866	7	3	2	67	4	2	50
5904	1	0	0	0	1	1	100
5906	2	2	2	100	0	0	0
5909	1	1	1	100	0	0	0
5919	2	1	0	0	1	1	100
5920	4	2	2	100	2	2	100
6109	12	6	4	67	6	3	50
6327	1	1	0	0	0	0	0
6377	2	1	1	100	1	0	0
6390	2	1	1	100	1	1	100
6506	19	9	8	89	10	10	100
6507	26	13	11	85	13	10	77
6508	1	0	0	0	1	1	100
6509	21	10	6	60	11	7	64
6510	16	8	7	88	8	7	88
Total	158	79	53	67.1	79	55	69.6

Medical officer's comments:
Only 4 of 36 US sites (5752, 5754, 5866, 6109) randomized more than 5 patients into the trial and only 1 US (6109) site randomized more than 10 patients into the trial. The 5 South Africa sites (6506-6510) that participated in the trial accounted for 40/79 (50.6%) and 43/79 (54.4%) patients enrolled in the trovafloxacin and cefoxitin/doxycycline arms, respectively; 32/53 (60%) and 35/55 (64%) of the evaluable patients in the alatro/trova and cefoxitin/doxycycline arms, respectively, were from these same South African sites.

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Table 122.2 Summary of Subject Disposition

	Alatrofloxacin ↓ Trovafloxacin	Cefoxitin/Doxycycline ↓ Doxycycline
	Number and Percentage (%) of Subjects	
Randomized Subjects	79	79
All Treated Subjects	79 (100%)	79 (100%)
Withdrawn from Treatment[a]	23 (29%)	10 (13%)
Completed Treatment	56 (71%)	69 (87%)
Withdrawn from Study	19 (24%)	17 (22%)
Withdrawn during Treatment	12 (15%)	8 (10%)
Withdrawn during Follow-Up	7 (9%)	9 (11%)
Completed Study	60 (76%)	62 (78%)
Completed Treatment and Study	49 (62%)	60 (76%)
Evaluated for Efficacy		
Clinical Intent-to-Treat	79 (100%)	79 (100%)
Clinically Evaluable	53 (67%)	55 (70%)
Bacteriological Intent-to-Treat	51 (65%)	49 (62%)
Bacteriologically Evaluable	31 (39%)	33 (42%)
Assessed for Safety		
Adverse Events	79 (100%)	79 (100%)
Laboratory Tests	75 (95%)	77 (97%)

a Of the subjects withdrawn from treatment, 11 alatrofloxacin/trovafloxacin and 2 cefoxitin/doxycycline → doxycycline subjects completed study.

Medical officer's comments:
Fewer patients in the alatro/trova arm completed the study and treatment when compared with the cefoxitin/doxycycline arm.
Based on the applicant's calculations (outlined in the Statistical considerations section on page 12) 142 evaluable patients were needed per arm; however, only 79 patients were randomized to each of the treatment arms. Of the 79 subjects each in the alatro/trova and cefoxitin/doxycycline arms, 67% and 70% were clinically evaluable respectively, and 39% and 42% bacteriologically evaluable, respectively.

Table 122.3 Summary of Premature Discontinuations From Treatment (All Treated Subjects)		
	Alatrofloxacin ↓ Trovafloxacin (N=79)	Cefoxitin/doxycycline ↓ Doxycycline (N=79)
	Number and Percentage (%) of Subjects	
Total Discontinued	23 (29%)	10 (13%)
Discontinuations Related to Study Drug:	12 (15%)	2 (3%)
Adverse Event	4 (5%)	1 (1%)
Insufficient Response	8 (10%)	1 (1%)
Discontinuations Unrelated to Study Drug:	11 (14%)	8 (10%)
Adverse Event	3 (4%)	2 (3%)
Did not meet Randomization Criteria	1 (1%)	0
Lost to Follow-up	4 (5%)	5 (6%)
Other	1 (1%)	1 (1%)
Protocol Violation	1 (1%)	0
Withdrawn Consent	1 (1%)	0

Medical officer's comments:
More than twice as many patients in the trovafloxacin arm were discontinued from the study overall; discontinuations due to adverse events and insufficient response were more common in the alatro/trova arm.

Table 122.4 Summary of patients disqualified from efficacy analysis

	Alatrofloxacin/ Trovafloxacin	Cefoxitin/Doxycyline
Clinically Not Evaluable	26	24
No post- baseline clinical assessments	15	18
Insufficient Therapy	11	8
Prior Antibiotic Therapy	1	1
Concomitant Antibiotic Therapy	8	3
Intercurrent Illness	2	1
Surgical Intervention	1	3
Other	3	1
Bacteriologically Not Evaluable	22	22
No baseline pathogen	21	22
No post- baseline cultures	20	19

Medical officer's comments:
More patients in the alatro/trova arm were discontinued due to the use of concomitant antimicrobial therapy. Some of the reasons that concomitant antimicrobial agents were used included for an allergic reaction to study drug, and as therapy for trichomoniasis/bacterial vaginosis (metronidazole), respiratory tract infections, syphilis (procaine Penicillin G), and appendicitis.

After review of case report forms, patients disqualified from the analysis and patients who received concomitant antimicrobial therapy during the study, the reviewer accepted the applicant's evaluable population.

DEMOGRAPHICS

Table 122.5 Demographic Characteristics of Treated Subjects

	Alatro 200mg IV qd -> Trova 200mg PO qd	Cefox 2g IV q6h & Doxy 100mg IV q12h -> Doxy 100mg PO bid
Number of Subjects	79	79
Age (yr)		
16- 44	78(99%)	78(99%)
45- 64	1(1%)	1(1%)
Mean	27.4	26.8
Minimum	(b)(4)	
Maximum		
Race		
ASIAN	1(1%)	0
BLACK	50(63%)	62(78%)
COLOURED	0	1(1%)
HISPANIC	8(10%)	5(6%)
MIXED	8(10%)	4(5%)
WHITE	12(15%)	7(9%)
Weight (kg)		
Mean	62.3	64.1
Minimum	(b)(4)	
Maximum		
Missing	1	0

Medical officer's comments:
There were no significant differences between the two groups with regard to race, weight, and age distribution.

APPLICANT'S EFFICACY ANALYSIS

Table 122.6 Summary of Sponsor-Defined Clinical Response Rates at the End of Study Visit (Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=53)	Cefoxitin/doxycycline ↓ Doxycycline (N=55)	95% CI
	Number and Percentage (%) of Subjects		
End of Study:			
Number of Subjects Assessed	53 (100%)	55 (100%)	
Cure	43 (81%)	50 (91%)	(-22.8, 3.2)
Failure	10 (19%)	5 (9%)	

Medical officer's comments:
Equivalence was not demonstrated for treatment difference in clinical cure rates; at the end of study, the cefoxitin/doxycycline group had higher clinical cure rates in comparison to the alatrofloxacin/trovafloxacin group--- 91 vs. 81% respectively (95% CI with continuity correction: -24.6,5.1). An insufficient number of subjects were enrolled in this study.

To see if the difference in baseline severity as manifested by the presence of an adnexal mass had an effect on the treatment response, a subset analysis was performed. The results are summarized in the table that follows.

Table 122.7 Clinical Response Rates at the End of Study for Clinically Evaluable Subjects based on the presence/absence of adnexal mass (table provided by FDA statistician)

Subset	Alatro/Trova (N=53)	Control (N=55)	95% C.I.	P-value Breslow-Day
With Mass	13/20 (65.0%)	17/20 (85.0%)	(-51.1%, 11.1%)	0.616
Without Mass	30/33 (90.9%)	33/35 (94.3%)	(-18.8%, 12.0%)	
All	43/53 (81.1%)	50/55 (90.9%)	(-24.6%, 5.1%)	

Statistician's comments:
The Breslow-Day's test demonstrates that treatment effects were homogeneous (p-value=0.616) between the subjects with mass and the subjects without mass. Please note no conclusions could be drawn from the confidence intervals for the two subgroups due to the small numbers.

Medical officer's comments:
Comparison of the subsets shows a greater treatment difference in the group with a mass when compared with those without a mass, suggesting that the severity of illness may have been a factor in the clinical response in this study.
Since there were only 3 patients in the alatro/trova and there was 1 patient in cefoxitin/doxy groups with tubo-ovarian abscesses, no subset analysis was performed for patients with tubo-ovarian abscesses.

Table 122.8 Summary of Clinical Response Rates at the End of Study For the Most Frequently Isolated Baseline Pathogens[a] (Clinically Evaluable Subjects)

	Alatrofloxacin ↓ Trovafloxacin (N=53)	Cefoxitin/doxycycline ↓ Doxycycline (N=55)
Pathogen	**Number of Subjects**	
N. gonorrhoeae	11/18 (61%)	16/17 (94%)
Peptostreptococcus sp.	8/11	11/13
C. trachomatis	4/6	10/10
E. coli	5/5	4/5

a Includes ≥5 isolates of a given pathogen in any treatment group; percents displayed only when denominator is ≥15.
A subject could have had more than one pathogen isolated at baseline.

Medical officer's comments:
Only 11/18 clinically evaluable patients in the alatro/trova group with *N. gonorrheae* and 4/6 with *C. trachomatis* isolated at baseline were considered cured at follow-up, while the cure rates in the cefoxitin/doxycycline arm were 16/17 and 10/10 patients with *N. gonorrheae* and *C. trachomatis*, respectively.

Table122.9 Summary of the Differences Between Investigator-Defined and Sponsor-Defined Clinical Responses at Visit 3 and the End of Study (Clinically Evaluable Subjects)			
Subject Number	**Investigator Assessment**	**Sponsor Assessment**	**Reason**
Alatrofloxacin → Trovafloxacin:		**Visit 3**	
5602-0070	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 5)
6109-0136	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 4)
6507-0200	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 18)
6507-0301	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 20)
6507-0311	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 15)
6507-0313	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 13)
6510-0272	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 7)
Alatrofloxacin → Trovafloxacin:		**End of Study**	
5768-0013	Not Assessable	Failure	Failure (Day 15) carried forward
6109-0132	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 4)
6109-0136	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 4)
6507-0301	Cure	Failure	Concomitant antibiotics for inadequate response (Day 20)
6510-0272	Not Assessable	Failure	Concomitant antibiotic for inadequate response (Day 7)
Cefoxitin/doxycycline → Doxycycline:		**Visit 3**	
6507-0302	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 18)
6509-0232	Not Assessable	Failure	Concomitant antibiotics for inadequate response (Day 19)
Cefoxitin/doxycycline → Doxycycline:		**End of Study**	
5904-0137	Cure	Failure	Concomitant antibiotics for inadequate response (Day 31)
Ref: Appendix I, Table 2.4 and Appendix V, Table 16			

Medical officer's comments:
Following review of the case report forms for these subjects, the reviewer is in agreement with the applicant's assessment of outcome for these patients.

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SAFETY

Table 122.10 Summary of the Most Commonly Reported Adverse Events[a,b] by Body System - All Causality (All Treated Subjects)		
	Alatrofloxacin ↓ Trovafloxacin (N=79)	Cefoxitin/Doxycycline ↓ Doxycycline (N=79)
	Number and Percentage (%) of Subjects	
Number of Subjects With at Least One Adverse Event	57 (72%)	53 (67%)
BODY SYSTEM WHO Term		
APPL./INJ./INCISION/INSERTION SITE	15 (19%)	19 (24%)
Appl./Inj./Incision/Insertion Site Infection/Inflam.	10 (13%)	9 (11%)
Appl./Inj./Incision/Insertion Site Pain	2 (3%)	7 (9%)
CARDIOVASCULAR	10 (13%)	9 (11%)
Thrombophlebitis	5 (6%)	7 (9%)
CENTRAL AND PERIPHERAL NERVOUS	11 (14%)	8 (10%)
Headache	10 (13%)	6 (8%)
GASTROINTESTINAL	26 (33%)	17 (22%)
Abdominal Pain	7 (9%)	6 (8%)
Constipation	8 (10%)	6 (8%)
Nausea	14 (18%)	9 (11%)
Vomiting	9 (11%)	4 (5%)
REPRODUCTIVE	8 (10%)	12 (15%)
Vaginitis	3 (4%)	9 (11%)
SKIN/APPENDAGES	11 (14%)	3 (4%)
Pruritus	6 (8%)	1 (1%)

APPL./INJ./INCISION/INSERTION SITE = Application/Injection/Incision/Insertion Site

a ≥5 % of subjects in any treatment group.

b Includes data up to 7 days after last dose of active study medication

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Table 122.11 **Supplemental table of most common adverse events (provided by the FDA statistician)**

Safety	Trovafloxacin	Ofloxacin/Clindamycin	Fisher's p value
Central and Peripheral nervous system	11(13.9%)	8 (10.1%)	0.626
Dizziness	3 (3.8%)	2 (2.5%)	1.00
Headache	10 (12.7%)	6 (7.6%)	0.43
Discontinuations due to an AE	10/79 (12.7%)	4/79 (5.1%)	0.160
Clinically significant lab abnormalities	42/75 (58.3%)	44/77 (57.1%)	1.000

Medical officer's comments:
The differences in the adverse events for each group were not statistically significant. The rates of dizziness and headache were comparable between the two groups.

Laboratory result abnormalities
No subject in either treatment group was discontinued from treatment due to abnormal laboratory results. When corrected for baseline abnormalities, clinically significant post-baseline laboratory abnormalities were comparable between groups: 56% (42/75) in the alatrofloxacin/trovafloxacin group and 57% (44/77) in the cefoxitin/doxycycline group.

One subject (1%) in the cefoxitin/doxycycline group had clinically significant serum creatinine values; one subject (1%) in the alatrofloxacin/trovafloxacin group had clinically significant total bilirubin values; and three subjects (4%) in the alatrofloxacin/trovafloxacin group and two subjects (3%) in the cefoxitin/doxycycline group had clinically significant hemoglobin values.

Conclusions
An insufficient number of patients was enrolled in this study; equivalence was not demonstrated between alatrofloxacin/trovafloxacin and cefoxitin/doxycycline in the treatment of PID in hospitalized patients.

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